it is clear that specific written description of every chemical that might be screened in the methods is not required.

The specification provides more than sufficient written description of this screening method. For example, on page 8 of the specification at lines 20-28, the specification explains that the co-regulatory protein/nuclear receptor LBD coexpression system is useful for screening compounds that bind to nuclear receptors, compounds which have activity like a known ligand, and proteins that interact with ligands. In addition, page 9 of the specification, beginning at line 4, explains that the nuclear receptor binds to its target gene in conjunction with a co-regulatory protein and a ligand. The mechanism and theory behind two-hybrid screening assays are also described. The paragraph beginning at line 24 of that same page discusses the rationale for screening for chemicals, and the paragraph beginning at line 24 of page 10 discusses the rationale for screening for proteins. This paragraph specifically mentions that the two-hybrid assay is used to find a protein and a ligand which interact with each other. Applicants submit that the amendments to the claims are fully supported by the specification as filed.

Clearly, the specification describes an assay which, in one embodiment, can screen for both a protein and a chemical which together bind to the nuclear receptor or nuclear receptor LBD. The discussion in the specification is more than sufficient to describe the invention in such a manner that a skilled artisan would recognize Applicants were in possession of the claimed invention. Applicants have fully described and explained the rationale, theory and mechanism behind the claimed screening method, which method involves screening for a protein and a chemical. The identification of all the chemicals which may be screened is not necessary to put Applicants in possession of the invention since the screening method may be used to screen any chemical for the ability to interact (along with the protein also being screened) with the -SDPPSPS- co-regulatory protein, regardless of its structural characteristics or properties. The property of the chemical for which the screen tests, co-binding with the nuclear receptor or

nuclear receptor LBD and the co-regulatory protein, is fully described, and no other property of the chemical is relevant to the methods claimed.

Applicants therefore respectfully submit that the rejection under 35 U.S.C. § 112, first paragraph is not proper as to the claimed invention. Applicants request that this rejection be withdrawn.

Claims 43-52 also are rejected under 35 U.S.C. § 112, first paragraph, as lacking sufficient written description regarding the co-regulatory protein. The Office Action states that the claims encompass any protein of any amino acid sequence which comprises SEQ ID NO:5 or SEQ ID NO:9, however the portions of the amino acid sequence that is N-terminal or C-terminal to the specified sequences are not described. The Office concludes that additional representative sequences, beyond that of PNRC, which identify structural characteristics or properties beyond the binding motif of SEQ ID NO:5 or SEQ ID NO:9 are required to describe the co-regulatory protein. Applicants respectfully submit that this requirement is superfluous given the structure/function relationship of the co-regulatory protein binding motif as claimed. No skilled artisan would doubt, given the descriptions and experimental results in the specification as filed, that Applicants had possession of a screening assay for determining protein/chemical pairs which interact with co-regulatory proteins having the SDPPSPS core ligand motif since (1) that motif is exhaustively described in the specification, (2) that motif is the functional, active moiety of the co-regulatory protein, and (3) no other portion of the protein or peptide sequence N-terminal or C-terminal to the motif is relevant to the function of the protein being screened in the claimed method.

The specification provides ample description of the binding motif and the screens which employ it. For example, the discovery of the new family of nuclear receptor co-regulatory proteins in which ligand binding is effected by the SDPPSPS binding motif is described at page 8, lines 6-18. PNRC (SEQ ID NO:8) is only <u>one example</u> of proteins which have the SDPPSPS motif. Other clones were identified as described in the specification on page 17 at lines 11-15. These clones encoded a previously unknown protein with regional homology to PNRC. This other protein possessed the SDPPSPS

binding motif and this binding motif is the portion of the proteins which provides the function.

Further, truncated peptides of PNRC, having different regions N-terminal and C-terminal to the binding motif were tested for activity. The studies, reported in Example 6, demonstrate that the function of amino acid sequences extraneous to the SDPPSPS binding motif are not relevant to the function of the co-regulatory protein which is claimed. Any protein containing this motif can be used in the assays since it is the motif itself which imparts the binding ability for which the screen tests. Therefore, it is not necessary or reasonable to require that the structure or function of these non-relevant portions of the claimed co-regulatory sequences be described. The written description already fully describes the functional moiety of the proteins which it is desired to claim.

Therefore, Applicants respectfully submit that the specification contains sufficient written description such that a skilled artisan would readily know that Applicants had possession of a screening assay, as claimed, that can be used to screen for interaction with the functional domain or any sequence having the described functional domain. This is particularly so in light of the knowledge of the skilled artisan to the effect that other nuclear receptor co-regulatory protein families function in a similar manner using a common LXXLL motif which is necessary and sufficient to mediate the binding of these proteins to liganded nuclear receptors. See specification, page 2, lines 11-21. Applicants request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Claims 43-52 have been rejected under 35 U.S.C. § 112, first paragraph as not enabled by the specification in their full scope. The rejection is based on the assertion that the specification supports only claims directed to chemicals selected from the group consisting of estradiol, deoxycorticosterone, progesterone and retionic acid, and the protein PNRC consisting of SEQ ID NO:8. The Office has reasoned that undue experimentation would be required to perform the screening method with further chemicals or with any protein encompassing SEQ ID NO: 5 or SEQ ID NO:9.

Applicants submit, however, that no experimentation at all is required to screen chemicals beyond the four listed in the Office Action. The method is a screening method, and as discussed at length above with regard to the written description rejection, may be used to screen any chemical. The type, structure or function of the chemical to be screened is not relevant to the enablement of the method being claimed. Certainly not all chemicals will be found to interact with some protein in the screen, but active chemicals are not being claimed. The claims are directed to a screening method to find chemicals which do interact (with the proteins also being screened) with nuclear receptor co-regulatory proteins that bind to a nuclear receptor or nuclear receptor ligand binding domain and that have a region according to SEQ ID NO:5. Whether every chemical tested will yield a positive result in the screen, or whether all chemicals which do yield a positive result in the screen have been identified in the specification does not impact or whether the screening method is enabled.

Applicants respectfully submit that since the screen can be used to screen any chemical, and this is fully supported in the specification, for example at page 8, lines 20-26, that Applicants are not required to specifically describe every chemical which can be screened. Applicants are only required to enable the claimed method to screen the chemicals, and this they have done. Applicants therefore request that the rejection on this basis under 35 U.S.C. § 112, first paragraph be withdrawn.

Regarding the rejection of the claims as not enabled for co-regulatory proteins beyond SEQ ID NO:8, Applicants refer the Office to the discussion above pertaining to rejection of these same claims for lack of written description.

Applicants submit that the specification fully describes how to perform each step of the claimed screening method. Applicants have provided an example, showing the assay to work using the exemplary SDPPSPS comprising co-regulatory protein, PNRC. Applicants have also provided data showing that other, shorter sequences which contain the SDPPSPS binding motif also interact and thus could be used in the method. See, for example, Figure 5B. In particular, contrary to the Office assertions, PNRC/278-300 (SEQ ID NO:9) was found to interact with SF1 as does PNRC, see p. 17, lines 20-

21, and therefore obviously SEQ ID NO:9 can be used in the claimed screens. As described in the specification, the SDPPSPS motif is clearly necessary and sufficient for the interaction upon which the claimed screen is based. Any protein containing the SDPPSPS motif can be used to screen for interaction. The remaining portions of the co-regulatory protein are not relevant to the screen and do not affect the results since they do not relate in any way to the binding tested in the screen. A description of non-relevant proteins, either by structure or function and activity would not assist the skilled reader of this specification to perform the claimed methods because these non-relevant protein sequences do not have a function in this method. The guidance pertaining to the SDPPSPS motif and the screen methods themselves therefore is more than enough to enable a skilled artisan to perform the claimed screening method. Applicants would like to point out that the claims are drawn, not to co-regulatory proteins which can be used to screen, but to screening methods designed to screen chemical/protein pairs for the ability to interact with a particular recited family of co-regulatory proteins.

In summary, Applicants have provided descriptions of several proteins in this family and have described both structurally and functionally the active moiety that defines this family (i.e. the SDPPSPS motif). Peptides which comprise the SDPPSPS moiety, and which can be used in the method are described structurally and functionally. Applicants also have shown by experimentation that the SDPPSPS sequence is the functional moiety of the family of co-regulatory proteins described in the specification, and that no other functional moiety is required for the screen to work. Thus, no other portion of the SDPPSPS comprising protein would need to be described for the screening assay to be enabled. Applicants therefore request that the rejection of claims 42-53, now new claims 53-55 and amended claims 43-51 as not enabled be withdrawn.

Claims 43-52 are rejected under 35 U.S.C. § 112, second paragraph as indefinite. Applicants have rephrased independent claims 43 and 52 to make the invention more clear and avoid the phrase in the preamble which the Office Action specifically quotes. Applicants submit that the claims fully comply with 35 U.S.C. § 112, second paragraph

and maintain that the screening methods can be used with any chemical. Applicants therefore request that the rejection of the claims under 35 U.S.C. § 112, second paragraph be withdrawn.

In view of the foregoing amendments and discussion, the claims are believed to be in condition for allowance. Favorable action is earnestly solicited.

RESPECTFULLY SUBMITTED,			
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Attachments: Mark up of Claims

2124-311.am2

Mark-up of Claims:

44. (Amended) The method of claim [43] 53 wherein said co-regulatory protein is 35 kDa.

45. (Amended) The method of claim [43] 53 wherein said co-regulatory protein comprises SEQ ID NO:9.

46. (Amended) The method of claim [43] 53 wherein said co-regulatory protein comprises SEQ ID NO:8.

47. (Twice Amended) The method of claim [43] 54 wherein said nuclear receptor ligand binding domain and said [ligand or hormone] chemical are selected from the sets of (i) estrogen receptor and estradiol, (ii) glucocorticoid receptor and deoxycorticosterone, (iii) androgen receptor and dihydrotestosterone, (iv) progesterone receptor and progesterone, (v) thyroid hormone receptor and T3, (vi) retinoic acid receptor and all-*trans*-retinoic acid, and (vii) 9-cis-retinoic acid receptor and 9-*cis*-retinoic acid.

48. (Amended) The method of claim [43] 53 wherein expression of said reporter gene causes production of histidine.

49. (Amended) The method of claim [43] 53 wherein said reporter gene is CAT.

50. (Amended) The method of claim [43] 53 wherein said cells are yeast cells or human cells.

51. (Amended) The method of claim [43] 53 wherein said nuclear receptor is capable of binding to an aromatase gene.